EXPERIMENTAL INFECTIOUS ENDOCARDITIS.*

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The factors which determine infection of the endocardium are still quite obscure. A satisfactory explanation, based on experimental evidence, has not yet been offered as to why the valves are involved so much more frequently than the mural endocardium. While it is generally assumed that the bacteria localize by implantation, the greater frequency of mitral and tricuspid than semilunar endocarditis remains to be explained.

Köster[1] demonstrated that extension in an established human endocarditis may be due to embolism and suggested that endocarditis may begin as an embolic process. Experimental proof of this mode of origin is still lacking, however. Lissauer,[2] after an extensive review of the literature, concludes that while endocarditis may occur exceptionally as an embolic process, no one has been able to show experimentally that this mode of origin really plays a rôle in the localization of bacteria on the heart valves.

The great difficulty of producing endocarditis experimentally without previous injury to the valves is well known. Ribbert[3] produced endocarditis in rabbits by intravenous injections of emulsions of staphylococci and potato particles, and showed that the endocarditis was due, at least in some cases, to implantation. Orth and Wyssowitsch,[4] and Fulci[5] had similar results from injections of suspensions of staphylococci and also of streptococci with finely pulverized charcoal. These authors were not able, however, to produce endocarditis by intravenous injection without the foreign particles. Recently Lissauer obtained endocarditis in two of 20 rabbits after repeated intravenous injections of a non-virulent, white staphylococcus. One rabbit died in two months after six injections, the other in six months after 10 injections, both showing

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[1] *Virchow's Arch.*, 1878, 72, p. 257.

[2] *Cent. f. Allg. Path.*, etc., 1912, 23, p. 243.

[3] *Fortschritte der Medicin*, 1886, 4, p. 1.

[4] *Virchow's Arch.*, 1886, 103, pp. 300 and 333.

[5] *Beiträge z. Path. Anat.*, 1908, 44, p. 349.

small vegetations on the mitral and tricuspid valves. He offers no explanation as to why repeated injections over a long period should produce endocarditis.

Horder[1] has shown that the cocci cultivated from the blood in cases of chronic infectious endocarditis as well as allied streptococci cultivated from the throat and feces are quite prone to produce endocarditis in animals. Other observers have had similar results. In previous papers I[2] have shown that the production of endocarditis by intravenous injections of organisms isolated from cases of endocarditis is due to peculiar qualities of the bacteria. It is noteworthy that the form of endocarditis in question, namely, a chronic or subacute form which begins insidiously on a previously diseased valve, often with no demonstrable source of infection, and which nearly always runs a fatal course, is due to bacteria of very low virulence. The various strains differ quite markedly in certain details, but at certain stages they all are freely susceptible to phagocytosis, adhere more or less markedly to the surface of solid media, grow in clumps in broth, and produce endocarditis quite regularly when injected intravenously in rabbits. When injected in other regions they produce only slight illness and are rapidly destroyed by phagocytosis.

Certain experiments will now be described, the results of which seem to throw light on some of the problems connected with this form of endocarditis.

1. *Experiments with pure cultures of cocci isolated from cases of chronic infectious endocarditis.*—Practically all injections were made into the marginal ear vein of half-grown rabbits. Five strains of the cocci used were isolated from the blood and two from the tonsils of cases of subacute or chronic infectious endocarditis. All produced a variable amount of green on blood agar plates, all fermented inulin at one time or another, and at the time of the experiments the growths adhered to the surface of blood agar and formed clumps in broth. All the strains were freely susceptible to phagocytosis and non-virulent in the usual sense. Suppuration and diffuse peritonitis could not be produced. The

[1] *Quart. Jour. of Med.*, 1909, 2, p. 289.

[2] *Jour. Infect. Dis.*, 1909, 6, p. 245, and 1910, 7, pp. 411 and 429.

cocci injected were usually grown both on blood agar and in ascites-dextrose-broth; in the latter case, the cocci were removed and suspended in suitable amounts of salt solution. The dose, relatively speaking, in most instances was exceedingly large, so large that the amount of the injected material was often sufficient to kill in 24 hours.

In Table 1 are given the essential facts that illustrate the results obtained. We see that the localization on the valves is an embolic process and not due to implantation. The clumps of bacteria lodge in the capillaries, produce hemorrhage, and probably because of the relatively slight vascularity in the valves the organisms grow into clumps before leukocytes are able to cause their destruction. Hemorrhages and endocarditis occur at the apex of papillary muscles in the same way. Hemorrhages occur at the base of the semilunar valves also, and vegetations have been seen to grow from this region (Plate 1, Figs. 4 and 5). In the rabbits which died or were killed soon after the injection, hemorrhages were observed in all experiments as follows: tricuspid valve, 28 times; mitral, 9 times; base of aortic semilunar valve, 4 times; base of pulmonary semilunar valve, 3 times; in papillary muscles (chiefly at apex), 20 times; kidney, usually glomerular, 11 times; subendocardial (other than papillary or valvular), 4 times; lungs, 7 times. General subserous hemorrhages were seen 6 times. Valvular hemorrhages occurred repeatedly without hemorrhages elsewhere. This was especially true if the dose was not sufficient to kill the animal in 24 to 48 hours.

On the injection of doses so large that the animal would die in a few minutes marked cardiac, renal, and pulmonary hemorrhages would result, but in no such instance were valvular hemorrhages observed. A certain time must elapse before the valvular hemorrhage takes place.

After having established the close relation between hemorrhage and endocarditis in the rabbit, I made a similar study in guinea-pigs. Valvular hemorrhages were observed only twice and endocarditis failed to develop, due no doubt to the absence of blood supply in the valves of this animal.

To emphasize further the great affinity of these cocci for the

TABLE 1.

EXPERIMENTS WITH COCCI FROM CHRONIC OR SUBACUTE INFECTIOUS ENDOCARDITIS IN MAN.

Number of Rabbit	Intravenous Injections*	Time of Death after First Inoculation	Postmortem Examination
203.....	One very large dose of strain 1	24 hours	Hemorrhage at base of semilunar cusp (Plate 1, Fig. 4), and at apex of two papillary muscles in left ventricle, also in kidney, chiefly in glomeruli. Myocardium, gray; fatty degeneration of liver. Heart's blood, spleen, and surface of valve sterile. From hemorrhagic areas, pure cultures of organism injected.
221.....	One very large dose of strain 632	24 hours	Four hemorrhages in tricuspid valve, three along line of closure, the other, which is larger, is nearer base but extends to within 2 mm. of the free margin (Plate 1, Fig. 1). Two small hemorrhages in mitral valve. No hemorrhages anywhere else. Myocardium, gray and flabby. Right ventricle, dilated.
255.....	One large dose of strain B	48 hours	Four small hemorrhages of tricuspid valve and base of middle aortic semilunar cusp. Localized endocarditis of tricuspid valve and apex of papillary muscle. Four small vegetations are seen growing out of areas of hemorrhage.
191.....	Three medium-sized injections of strain 632 before and after animal passage	10 days	Vegetative tricuspid and mural endocarditis: thrombophlebitis of coronary vein; pulmonary infarction; peribronchial lymphadinitis. Original organism from vegetation and blood; typical encapsulated pneumococci from lymph glands and lung.
226.....	Two large doses of strain 632	9 days	Killed by ether. Vegetative endocarditis of tricuspid valve and apex of papillary muscle of left ventricle, cultures of which are positive. Blood, sterile. Ulceration along line of closure.
185.....	Three very large doses of strain E after four animal passages	14 days	Vegetative mitral and aortic endocarditis. Cultures yield organism injected.
189.....	One very large dose of strain E after seven animal passages	7 days	Vegetative tricuspid endocarditis; acute splenitis. Organism isolated resembles one injected.
182.....	Two medium-sized doses of strain E after three animal passages	10 days	Mitral and tricuspid endocarditis. Localized peritonitis. Organism isolated like one injected.
240.....	Two large doses of strain 657	22 days	Vegetative tricuspid, mitral, and mural endocarditis. The vegetation of the tricuspid orifice so large as to cause death by obstruction. The mural endocarditis involves the apices of the papillary muscles. The origin of these areas and the smaller vegetations are clearly subendothelial. The organism isolated from vegetation resembles closely the one injected.
237.....	One large dose of mixture of 10 strains, cultivated on blood agar for from three months to eight years	11 days	Mural endocarditis at apex of capillary muscle of right ventricle. Blood and joint fluids, sterile.

TABLE 1.—*Continued.*

EXPERIMENTS WITH COCCI FROM CHRONIC OR SUBACUTE INFECTIOUS ENDOCARDITIS IN MAN.

Number of Rabbit	Intravenous Injections	Time of Death after First Inoculation	Postmortem Examination
197.....	One very large dose of strain E after nine animal passages	8 days	Tricuspid, mitral, and mural endocarditis; miliary infarct of kidney; multiple pulmonary infarction, and pneumonia. Blood and spleen, sterile; vegetation and infarct in kidney yield coccus injected, while lung yields typical pneumococci.
188.....	Four large doses of strain E after seven and eight animal passages	8 days	Tricuspid and mural endocarditis; bronchopneumonia. Cultures from heart's blood negative; vegetation yields mostly cocci like the original and without virulence for guinea-pigs; lung and bone marrow yield pure cultures of an encapsulated, green-producing, inulin-fermenting diplococcus which kills guinea-pigs and rabbits.
223.....	One very large dose of strain E after eight animal passages	20 days	Massive vegetative endocarditis of tricuspid valve. Edema, hydroperitoneum, hydropericardium, and hydrothorax. Organism from vegetation resembles the one injected; pleural fluid gives pure culture of lanceolate, encapsulated diplococcus.
184.....	Two large doses of strain E after eight and nine animal passages	11 days after the first and one day after second injection	Pneumococcemia, acute splenitis; spleen yields typical pneumococci which kill rabbit in 24 hours from pneumococcemia.
209.....	One large dose of strain E after 10 animal passages	7 days	Killed. Healing mural and tricuspid endocarditis. Heart's blood, sterile. Crushed healing vegetation yields a few colonies of organism resembling the one injected.
208.....	Two large doses of strain E after 10 animal passages	24 days	Killed. Healing mural endocarditis of tip of papillary muscle of left ventricle. Heart's blood and healing area, sterile.
192.....	Two large doses of strain 632	50 days after first and one day after second injection	Healed localized endocarditis of mitral valve (see Plate 1, Fig. 6).
198.....	One very large dose of strain 632 after heating to 60° C. for one hour	24 hours	Hemorrhages in tricuspid and papillary muscle; cultures negative.
202.....	Three very large doses of strain 632 heated to 60° C. for one hour	17 days	Killed. Number of flattened, puckered, grayish areas in mitral valve, that is, healed endocarditis.

endocardium, the results obtained with two strains may be given. Strain 632 was injected intravenously in 32 rabbits; valvular hemorrhages were obtained 19 times; vegetative endocarditis, 6 times; healing or healed endocarditis, twice; pneumonia and endocarditis, 3 times; pneumonia alone, 3 times; and no gross lesions, 3 times. Strain E was injected into 22 rabbits; valvular hemorrhages were obtained 7 times; vegetative endocarditis, 6 times; healing or healed endocarditis, twice; pneumonia and endocarditis, twice; pneumonia only, 3 times; and no lesions, twice.

Hemorrhages and scars of the valves have been produced by the injection of cocci killed by heating to 60° C. for one hour. In five instances unmistakable evidence of healing or healed endocarditis was obtained (see Plate 1, Fig. 6). Three of these were found in the tricuspid and two in the mitral valve.

Microscopic sections of valves and papillary muscles, the seat of hemorrhages, show dilated blood vessels, desquamation of endothelial cells, and subendothelial and muscular extravasation of blood. What appears to the naked eye as subendothelial hemorrhages in valves and papillary muscles always proves to be such on microscopic examination (see Plate 2, Fig. 7). Bacterial emboli are not found in the areas of hemorrhage and the adjacent capillaries within 24 hours after the injections; at the end of 48 hours, however, bacterial masses are easily found, usually adjacent to an area of hemorrhage (see Plate 2, Fig. 8). At this time there is hardly any leukocytic infiltration about the bacterial masses, which is in marked contrast to the lesions in the glomeruli of the kidney in which leukocytic infiltration is marked at the end of 48 hours. In no instance is there any evidence of thrombosis at this early stage nor evidence that leukocytes were the carriers of bacterial clumps.

The lesions of the kidney in this experimental endocarditis in the rabbit are not unlike those described first by Aschoff[1] and Gaskell,[2] and more recently by Baehr,[3] in ulcerative or chronic infectious endocarditis in man. They consist essentially of glomerular hemorrhages due to bacterial emboli followed by leukocytic infiltration and later almost invariably by sclerosis. In two old rabbits, however, which were injected repeatedly and in which no endocarditis developed, some of these areas, instead of healing promptly, became the seat of minute, grayish-white masses made up of bacterial clumps, leukocytes, etc., similar to the endocardial vegetations. The hemorrhages occur almost exclusively in the fine capillaries of the glomerular tuft. At the end of 48 hours leukocytic infiltration may extend beyond Bowman's capsule. At the time of death from endocarditis in the rabbit fresh renal hemorrhages are rare, but healing or fibrous glomeruli are commonly observed. Red blood corpuscles have been found in the urine.

[1] *Pathol. Anat.*, Jena, 1911.

[2] *Jour. of Path. and Bact.*, 1912, 16, p. 283.

[3] *Jour. Exper. Med.*, 1912, 15, p. 330.

Table 1 shows an interesting fact which is in harmony with results obtained previously. After repeated animal passage these strains of cocci change into pneumococci, both as regards form and pathogenic power. As virulence increases, clump formation disappears, they no longer adhere to solid media, and only rarely produce endocarditis, but, instead, cause death from bacteriemia or pneumonia. Fatal pneumococcemia without localization was observed 11 times; bronchopneumonia, 7 times; and lobar pneumonia, 5 times. The strains isolated from the animals with pneumonia on further animal passage produced rapidly fatal pneumococcemia and not pneumonia. Pneumonia and endocarditis were observed in the same animals 5 times. The organisms isolated from the lung and peribronchial lymph glands in each instance resembled typical pneumococci while those from the depths of vegetations resembled closely the endocarditis strains. One experiment will serve to illustrate how the results were obtained: Strain E was easily differentiated from typical pneumococci by means of blood agar plates; it produced grayish-white colonies which adhered moderately, and which were surrounded by a very narrow zone of green. The strain used was grown from a single organism isolated for me by Mr. Moon by the Barber method. A medium-sized rabbit was given two intravenous injections, five days apart. The strain was then rapidly passed through a series of nine animals. A moderately sized dose was injected, the cocci now appearing to be typical pneumococci. The rabbit died in four days with vegetative aortic endocarditis and lobar pneumonia. The blood after death was sterile. From the lung, peribronchial lymph glands, and spleen pulp, pure cultures of typical pneumococci were isolated. From the depths of the vegetation the original endocarditis coccus was obtained in pure culture and from the superficial layers of the vegetation, both varieties.

In this connection I may state that Dr. Dochez, of the Rockefeller Institute for Medical Research, to whom I am indebted for a subculture of strain E, noted a number of months previously a similar reversion to the characteristics of typical pneumococci as virulence was restored by animal passage.

Lobar or bronchopneumonia was produced with each of the

strains as the virulence attained a certain point through animal passage. This result corresponds with the observations of Wadsworth[1] who found that in order to produce pneumonia in rabbits with pneumococci, a properly balanced relation between virulence and resistance of the host is necessary. Pneumonia was especially apt to occur when the rabbit had been injected once or twice previously. This suggests the idea that sensitization probably played a rôle in the development of the pneumonia.

A series of guinea-pigs were injected with heated cocci of a strain obtained from endocarditis. Two weeks later they were injected intravenously with equal doses of heat-killed and living cocci of (1) the strain as obtained from the blood, (2) the same strain after it had been converted into a pneumococcus by animal passage, and (3) with a strain of virulent pneumococcus from the blood of a case of pneumonia. All the animals reacted with symptoms of immediate anaphylaxis. Those receiving the live cultures reacted more violently than those receiving the heat-killed cocci. The bacteria disappeared from the blood more rapidly in the sensitized than in the non-sensitized pigs. This result at once suggests the idea that because the strains from endocarditis sensitize guinea-pigs to typical pneumococci they must themselves be pneumococci. This, however, cannot be regarded as settling the question conclusively because I[2] have shown that the proteins of the streptococcus and the pneumococcus are so nearly alike as to sensitize for each other.

The marked change which is brought about in these organisms by animal passage and cultivation under varying conditions led to certain further studies. Six strains were selected. In order to meet the objection which might be raised that I was dealing with mixed cultures in my previous work—which, however, is unlikely—the growths used were obtained from single bacteria of each of the strains isolated by Mr. Moon by a modification of the Barber method. Four of the strains were obtained from the blood during life and one from the tonsil in cases of chronic infectious endocarditis; one strain came from the pus of an empyema where it was associated with *B. fusiformis*. They all resembled closely Schott-

[1] *Am. Jour. Med. Sci.*, 1904, cxxvii, p. 851. [2] *Jour. Infect. Dis.*, 1911, 9, p. 190.

müller's *Streptococcus viridans*. The four strains from the blood adhered more to the surface and produced less green. All the strains, grown in each instance from single bacteria, were made to take on the morphological, cultural, and pathogenic features of typical pneumococci. More animal passages were necessary with the ones obtained from the blood than with those from the throat and pus before changing to typical pneumococci. Each of 16 strains which I have studied in this way, obtained mostly from the blood in cases of endocarditis, though also from the throat and elsewhere, have been changed into pneumococci in this way. I know that the idea that these strains from endocarditis are modified pneumococci is not generally held, but in view of the facts cited, the conclusion is forced on me that the organisms which are isolated from this type of endocarditis, the organism designated by Schottmüller as *Streptococcus viridans* and by Horder as "saprophytic streptococci," are in reality pneumococci that have become attenuated and peculiarly modified as the result of environmental conditions. For this reason I doubt the advisability of applying a special name, such as "Endocardococcus," to these organisms as suggested by Libman. The various strains also differ quite markedly in important respects. Certain strains of staphylococci, and probably also of influenza bacilli, from endocarditis likewise show this affinity for the endocardium and tendency to clump formation, both these qualities being lost simultaneously.

2. *Experiments with cultures of cocci isolated from chronic infectious endocarditis mixed with cultures of streptococci.*—Fourteen medium-sized rabbits were injected intravenously with mixtures of endocarditis cocci and streptococci in order to observe the results (Table 2). The animals receiving the largest quantities of endocarditis cocci received the smallest quantities of streptococci and vice versa. The differentiation of these bacteria is easy on the blood agar plate. The organisms from endocarditis produce a small colony surrounded by a green area, the streptococcus a small colony surrounded by a wide clear zone of hemolysis. Hemorrhages in valves and papillary muscles which resembled in appearance, size, and location those following intravenous injection of pure cultures of the endocarditis strains were observed in all but one animal.

This latter animal died soon after injection. The hemorrhages in the valves seems to serve as a protection because the organisms lived longer here than elsewhere. In no instance were endocarditis

TABLE 2.

EXPERIMENTS WITH MIXTURES OF ORGANISMS FROM ENDOCARDITIS AND WITH STREPTOCOCCI.

NUMBER OF RABBIT	STRAIN AND SIZE OF INTRAVENOUS INJECTIONS		TIME OF DEATH AFTER INOCULATION	POSTMORTEM EXAMINATION
	Organism 632 from Endocarditis	Streptococcus		
239.....	Very large	$\frac{1}{2}$ of blood agar slant	24 hours	Small pulmonary hemorrhages; hemorrhage of tricuspid valve and apex of one papillary muscle in left heart. No other visible hemorrhages. Blood, spleen, and joint fluids gave hemolyzing colonies only. Crushed portion of hemorrhage in valve and papillary muscle, chiefly hemolyzing but also some green colonies.
233.....	Medium	$\frac{1}{100}$ of blood agar slant	24 hours	Multiple small and one large hemorrhage in leaflet of tricuspid valve. No other hemorrhages. Myocardium gray, flabby. Blood, sterile; knee joint, pure hemolyzing colonies; spleen, equal number of hemolyzing and green-producing colonies; washed valve, sterile; crushed valve, green-producing colonies only.
P 872.....	Medium	$\frac{1}{100}$ of blood agar slant	48 hours	Hemorrhages in leaflet of mitral and tricuspid valves, and apex of papillary muscle. Blood and spleen sterile; joints, small number of hemolyzing colonies; washed valve, sterile; crushed area of hemorrhage, 10 green-producing colonies.
234.....	Medium	$\frac{1}{10}$ of blood agar slant	18 hours	Small hemorrhages in tricuspid valve. No other hemorrhages. Heart muscle, flabby, gray. Blood, very dark and clotted. Blood and spleen gave three times as many hemolyzing as green-producing colonies; joint, hemolyzing colonies only.
229.....	Small	One blood agar slant	48 hours	Hemorrhages in tricuspid valve and at base of one pulmonary semilunar cusp. Serofibrinous peritonitis and pleuritis. Myocardium, flabby, gray. Cultures yielded hemolyzing colonies from everywhere except crushed valve from which a few green colonies also developed.
232.....	Medium	$\frac{1}{10}$ of blood agar slant	12 days	Vegetative mural endocarditis at apex of papillary muscle right ventricle; arthritis right knee joint. Blood and spleen few, joint very many hemolyzing colonies. Surface of vegetation, chiefly hemolyzing colonies, from depth, green-producing colonies only.

cocci found in the joint fluids, and only four times in the blood and then in relatively small numbers. The streptococcus used was obtained from the throat in a case of tonsilitis. It had been cultivated on blood agar for three months and was only moderately

virulent. In the injected rabbits it was found usually in the blood and spleen and in every instance in the joints. Two rabbits in which the dose of endocarditis cocci was small developed arthritis without endocarditis. The hemolytic streptococcus was present in the joints in pure form early in the attack while later cultures were repeatedly negative even though the arthritis persisted for weeks. One rabbit (232, Table 2) developed both endocarditis and arthritis and the cultures here showed that the endocarditis coccus was responsible for the endocarditis and the streptococcus for the arthritis.

Five guinea-pigs, weighing from 200 to 250 gms., were also injected. One showed valvular hemorrhages, two developed arthritis, but none endocarditis. The hemolytic streptococcus was demonstrated soon after injection in large numbers in the joint fluids, while the endocarditis coccus was not found in any.

The results obtained furnish additional evidence to the effect that the arthritis in acute articular rheumatism may be due to hemolytic streptococci and suggest that the endocarditis may be due to the organisms which commonly produce endocarditis. It is possible, however, that in rheumatism streptococci are concerned which are intermediate between these two groups and which may produce both endocarditis and arthritis. Indeed the work of Poynton and Payne[1] and others points strongly in that direction.

3. *Experiments with mixed aerobic and anaerobic cultures of cocci from the throat.*—A series of experiments was made by injecting rabbits intravenously with mixed aerobic and anaerobic throat cultures grown on blood agar slants. The cultures were obtained from normal tonsils and from the tonsil of a case recovering from an attack of Vincent's angina. The aerobic cultures contained the green-producing, clump-forming cocci in predominating numbers ("Streptococcus viridans"), the micrococcus catarrhalis, and staphylococcus in large numbers, the micrococcus tetragenus, and a gram-negative bacillus; the cultures from the case of Vincent's angina contained in addition a few colonies of hemolytic streptococci. The anaerobic cultures contained the above strains and in addition the bacillus fusiformis. Three small rabbits were injected each

[1] *Lancet*, 1900, 2, p. 861.

with the aerobic cultures from four to six blood agar slants. Two died in 24 hours. Both showed valvular hemorrhages. The third died in six days from vegetative endocarditis of the tricuspid valve. The cultures of the blood and the surfaces of the valves in the first two animals showed a few staphylococci and the micrococcus catarrhalis, while from the crushed areas of hemorrhage there developed almost a pure culture of green-producing coccus; the cultures from the blood and vegetation of the rabbit which died of endocarditis developed this coccus in pure form. Four rabbits were injected with the anaerobic cultures, one with cultures from the normal throat and three with those from Vincent's angina. The former died of endocarditis at the end of seven days, cultures from vegetations and blood yielding a pure growth of the green-producing coccus. The other three also developed endocarditis. One rabbit (270) died in 72 hours. It showed fading hemorrhages in the valves and papillary muscle, and beginning vegetations. Cultures from the blood were sterile, while both anaerobic and aerobic cultures from the crushed valve yielded the green-producing coccus in pure form. A rabbit (265), which was injected three times in 10 days, died of a large thrombotic growth originating in the tricuspid valve. Smears and anaerobic cultures yielded both the bacillus fusiformis and the coccus. The third rabbit, (280) which was injected only once, was killed at the end of five days. A vegetative tricuspid and mural endocarditis was found. The cultures and smears gave the coccus in pure form.

4. *Experiments with mixed cultures of "Streptococcus viridans" and the bacillus fusiformis, and with the bacillus fusiformis only.*— The experiments showed that the hemorrhages found at the end of 48 hours as well as the endocarditis were due to the coccus and not to the bacillus fusiformis because the latter was absent in all the cultures and because neither hemorrhages nor endocarditis could be produced by injections of the latter in pure culture.

GENERAL CONSIDERATIONS AND CONCLUSIONS.

Endocarditis, caused by streptococci or pneumococci, and which develops in the course of a severe infection, runs a rapidly fatal course. Hence it does not seem likely that the simple or benign

forms of endocarditis, following streptococcus tonsilitis for example, or developing in the course of chorea or rheumatism can be due to highly virulent bacteria, but must be due rather to such cocci as produce endocarditis in rabbits. The same holds true for cases of unrecognized endocarditis in the young which later leads to valvular disease (nearly always mitral regurgitation with more or less stenosis). In the light of my experiments the sclerosis of the valves in such cases may be due either to repeated hemorrhages in the valves from bacterial emboli or, what is more likely, to a mild infection which gives no noteworthy clinical symptoms.

Endocarditis is more common in the young than in adults. In the light of my experiments the greater susceptibility of the endocardium in children may be explained as due to the presence of capillaries in the valves at this age. The attacks are relatively mild, blood cultures sterile, and recovery ensues, leaving a damaged valve. The very nature of these attacks makes it almost certain that the microorganisms in question are of a low grade of virulence. Now it is a well known fact that the chronic, malignant endocarditis under special consideration is ingrafted almost invariably on a previously diseased and sclerosed valve. My results suggest strongly that the same type of organisms can produce both the simple endocarditis and the fatal or malignant form when ingrafted on an old lesion. In the former case conditions for repair are better and healing results before the vegetations ulcerate. During the attack the valve becomes vascularized, but later scar formation ensues and the valve now becomes relatively avascular, contains exceedingly fine capillaries, and a condition is established which predisposes to reinfection. On account of the sclerosed condition of the valve, repair is more difficult, the vegetations grow large, ulceration takes place, and death eventually results. The fact that efforts at healing (sclerosis, calcification) even in the fatal cases in man are often present, as pointed out by Libman, together with the fact that I have produced simple endocarditis and sclerosis of valves experimentally, with cocci from chronic forms of endocarditis, speaks in favor of the view that, contrary to what is assumed on clinical ground, the organisms which produce the fatal form of the disease may also produce different grades of simple or benign endocardial inflammation.

The results of these experiments show that the endocarditis in the rabbit which follows injection of cocci which I believe to be modified pneumococci, is due to an embolic process. There is produced first valvular hemorrhage from which vegetations develop. The localization in the endocardium of the cocci from cases of chronic infectious endocarditis and of allied cocci from the throat, is due in large part to the presence of fine capillaries in the valves and to the peculiar mode of growth of the cocci. The relatively avascular structure of the valve serves to protect the cocci from leukocytes long enough to allow them to develop so as to produce the characteristic clumps around which fibrinous or other material is precipitated which for mechanical reasons again serves to protect the organisms. The production of valvular hemorrhages and of endocarditis by the simple intravenous injection of these cocci is an almost constant result so long as they form clumps and adhere to surfaces, but almost unattainable when this property has been lost either from artificial cultivation or animal passage.

It is necessary to inject intravenously an exceedingly large dose or smaller doses repeatedly in order to cause fatal endocarditis in rabbits. Otherwise healing results. Half-grown rabbits yield the best results, it being difficult to produce endocarditis at all in old rabbits, while in the very young, healing is more apt to occur.

The affinity of the endocarditis strains of cocci for the endocardium and of streptococci for joints is shown by the results of injections of mixtures of these organisms, and the exact cause of such affinity is unknown.

The injection of mixed aerobic and anaerobic cultures from the tonsils is followed by valvular hemorrhages and endocarditis, due to the presence of cocci similar to those found in chronic infectious endocarditis. The bacillus fusiformis does not seem to cause endocarditis in the rabbit.

The conclusion drawn in my earlier papers that the cocci in question are modified and attenuated pneumoccoci has received additional support because growths from single cocci from strains isolated originally from the blood of cases of endocarditis as well as from throats, when passed through animals, take on cultural and pathogenic properties indistinguishable from those of typical pneumococci.

My results also suggest strongly that the organisms belonging to this group may cause various forms of endocarditis designated as "simple infective endocarditis" in man as well as the malignant form of chronic infectious endocarditis.

EXPLANATION OF PLATES.

PLATE 1.

FIG. 1.—Photograph of a heart showing three hemorrhages in tricuspid valve of rabbit 221 (see Table 1). Portion showing the largest hemorrhage was cut out and sectioned (see Plate 2, Fig. 8).

FIG. 2.—Hemorrhages into tricuspid valve. Death 24 hours after a very large intravenous injection of strain 632.

FIG. 3.—Tricuspid and mural endocarditis. Ulceration has taken place on the side of closure. Death nine days after a large intravenous injection of strain E.

FIG. 4.—Subendothelial hemorrhage at base of semilunar cusp of pulmonary valve.

FIG. 5.—Vegetative endocarditis of aortic valve growing from base of cusps.

FIG. 6.—Healed, localized endocarditis of mitral valve, showing scars, thickenings, and some puckering of valve leaflet.

PLATE 2.

FIG. 7.—Subendothelial hemorrhages of tricuspid valve; death 24 hours after intravenous injection. Note the marked extravasation of blood, absence of leukocytic infiltration, and the intact endothelium on both surfaces of the valve. Hematoxylin and eosin. 250 diameters.

FIG. 8.—Photomicrograph of an early vegetation in the tricuspid valve, 48 hours after an intravenous injection. Note the many diplococci to the right of a small hemorrhage between the endothelial cells, and the absence of leukocytes. 800 diameters.

FIG. 9.—Photomicrograph of vegetation of tricuspid valve nine days after intravenous injection. The round masses at bottom are bacteria surrounded by a wide zone of leukocytic infiltration. Endothelium still intact, but encroached upon. Ulceration has not yet taken place. 120 diameters.

PLATE 1.

FIG. 1.

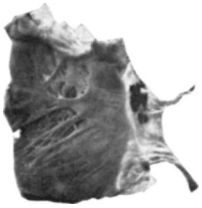

FIG. 2.

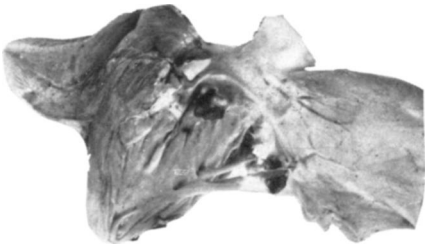

FIG. 3.

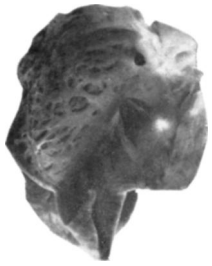

FIG. 4.

FIG. 5.

FIG. 6.

PLATE 2.

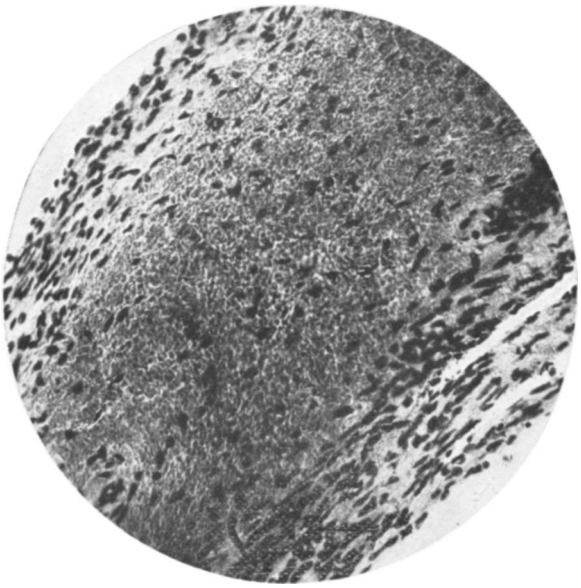

FIG. 7.

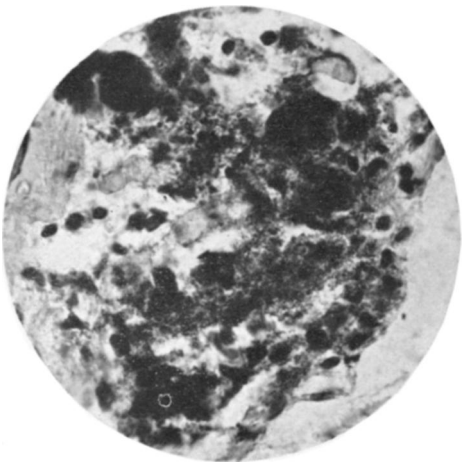

FIG. 8.

FIG. 9